Development of Dosimetry Model and Response Analyses

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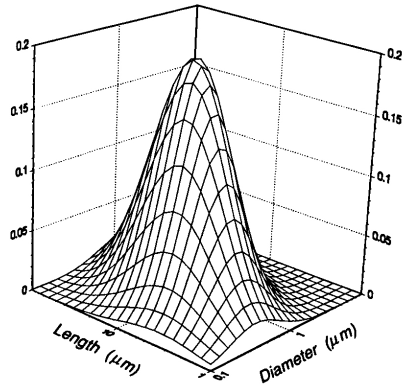
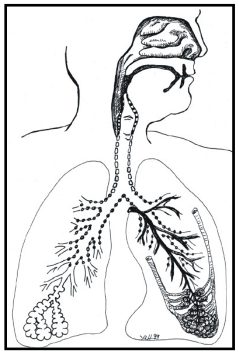
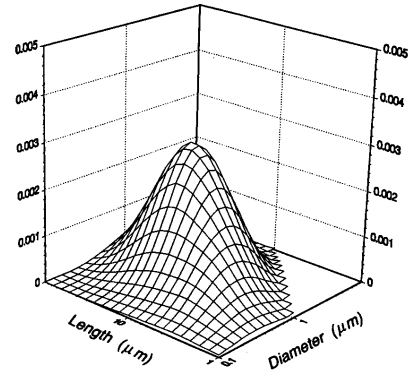
Outline

- Why
- What
- How
- Conceptual considerations
  - Anatomy
  - Physiology
- Role in risk assessment
- Summary

Why: Motivation for Modeling







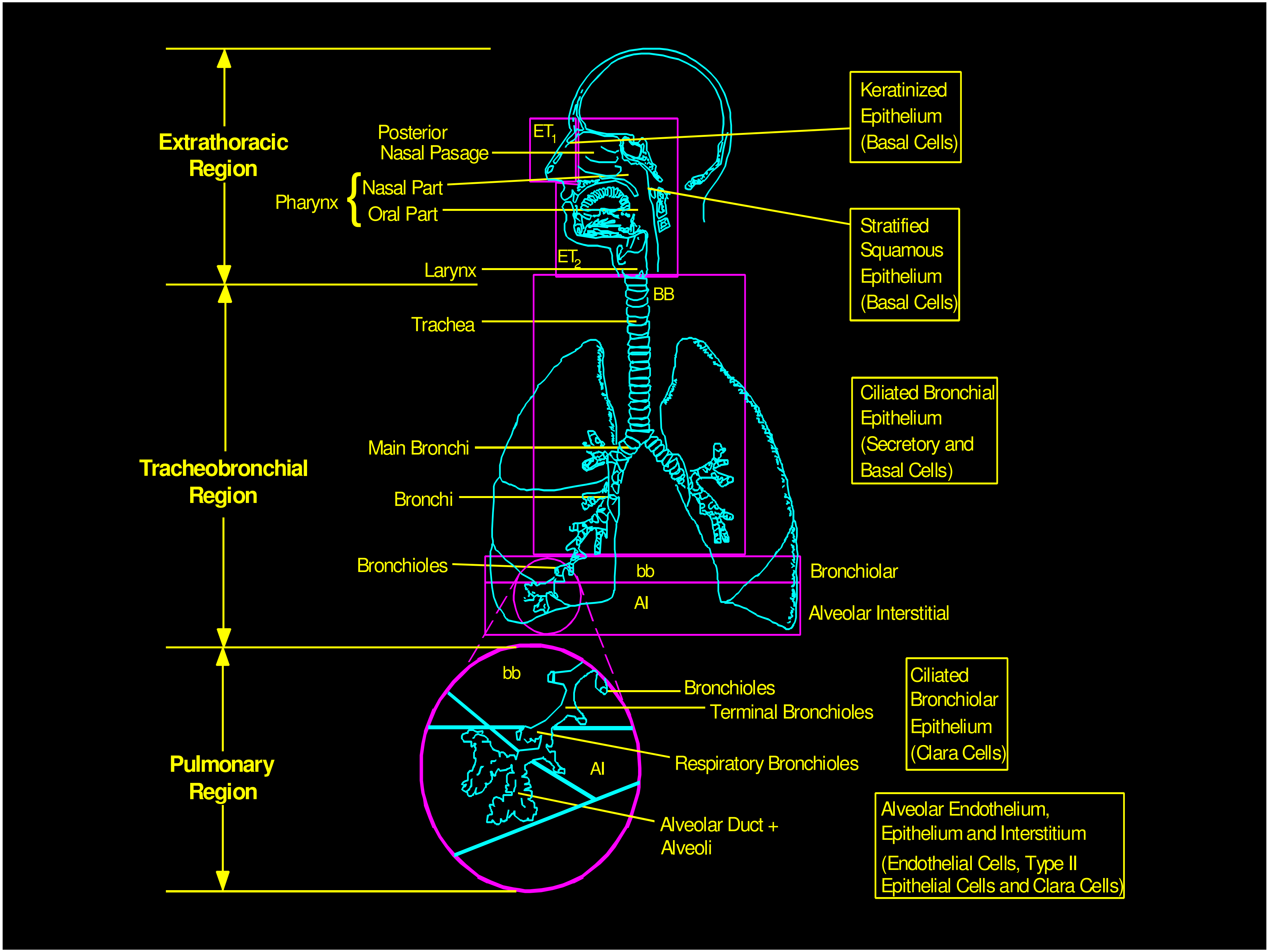
- External exposure ≠ Internal dose (i.e., lung burden)
- Keep up to date with latest biological understanding and testing measures
- Provide insights on important properties
  - Type: Libby amphibole versus others (e.g., chrysotile, ceramic, glass)
  - Size: Distribution of fibers and associated toxicity
  - Persistence: Role of splitting, dissolution and translocation
- Address differences between test species and humans
- Quantify and explore systematically

What: Definition of Dosimetry Modeling

- "Dose"
  - Internal body amount
  - Defined as associated with toxicity to evaluate "dose-response" relationship
- "Metric"
  - Measurement
  - Scale same as observation or response endpoint (e.g., lung region versus local, specific cell type)
- "Model"
  - Mimic or describe important processes
  - Simulate different exposure scenarios

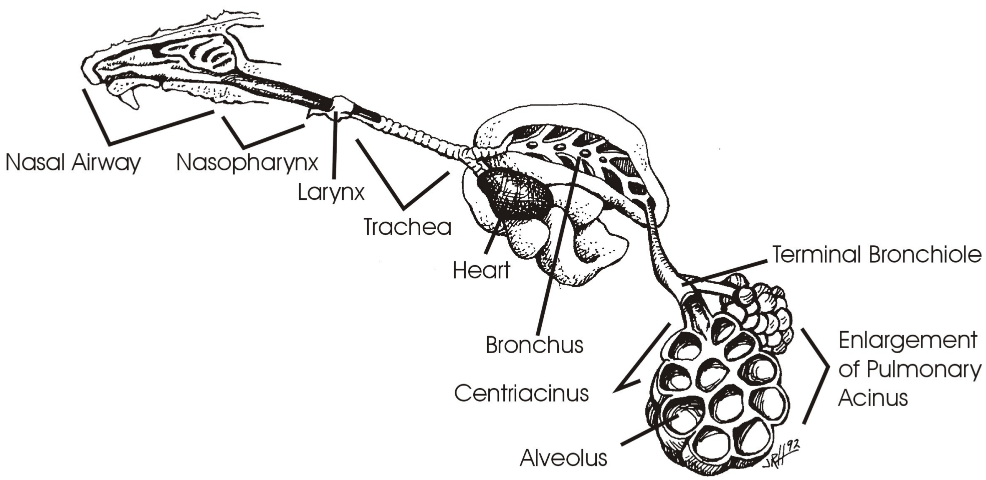
How: Modeling Approach

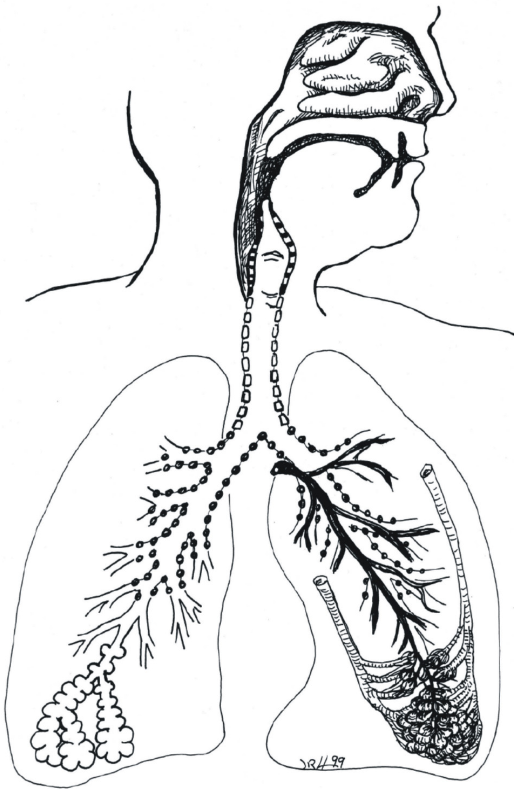
- Qualitative concept of process: Mode of action
  - Retained dose or lung burden = deposition - clearance
- Mathematical description of process using key determinants as parameters
  - Anatomy
  - Physiology
- Basic biological data in each species to support parameter values
- Verification of model structure against experimental data



Extrathoracic Region
Tracheobronchial Region
Pulmonary Region
Posterior Nasal Pasage
Pharynx
Nasal Part
Oral Part
Larynx
Trachea
Main Bronchi
Bronchi
Bronchioles
ET1
ET2
BB
bb
AI
Bronchiolar
Alveolar Interstitial
Keratinized Epithelium (Basal Cells)
Stratified Squamous Epithelium (Basal Cells)
Ciliated Bronchial Epithelium (Secretory and Basal Cells)
bb
Bronchioles
Terminal Bronchioles
Respiratory Bronchioles
AI
Alveolar Duct + Alveoli
Ciliated Bronchiolar Epithelium (Clara Cells)
Alveolar Endothelium, Epithelium and Interstitium
(Endothelial Cells, Type II Epithelial Cells and Clara Cells)

Model Structure: Airway Architecture



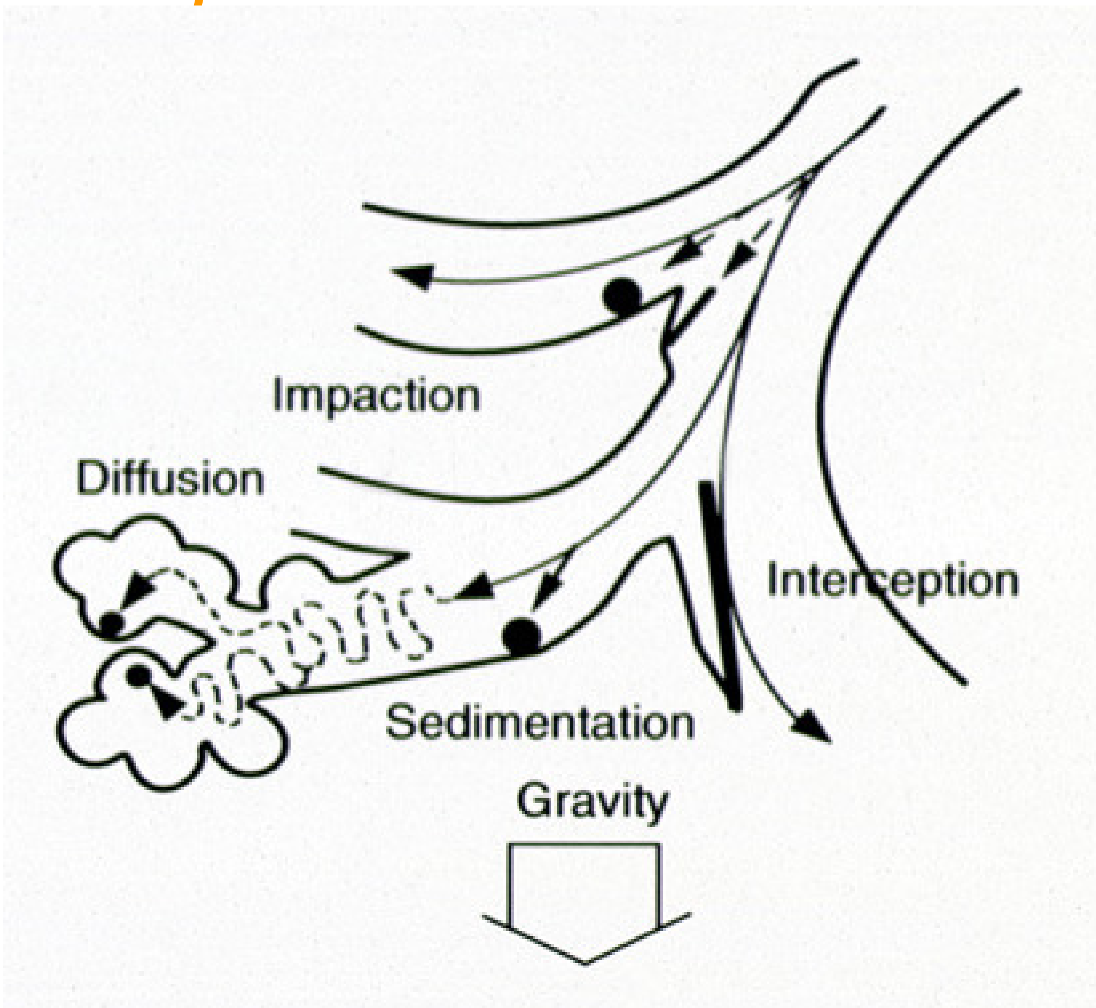


Illustrations courtesy of Dr. Jack R. Harkema, Professor of Comparative Pathology, Michigan State University.

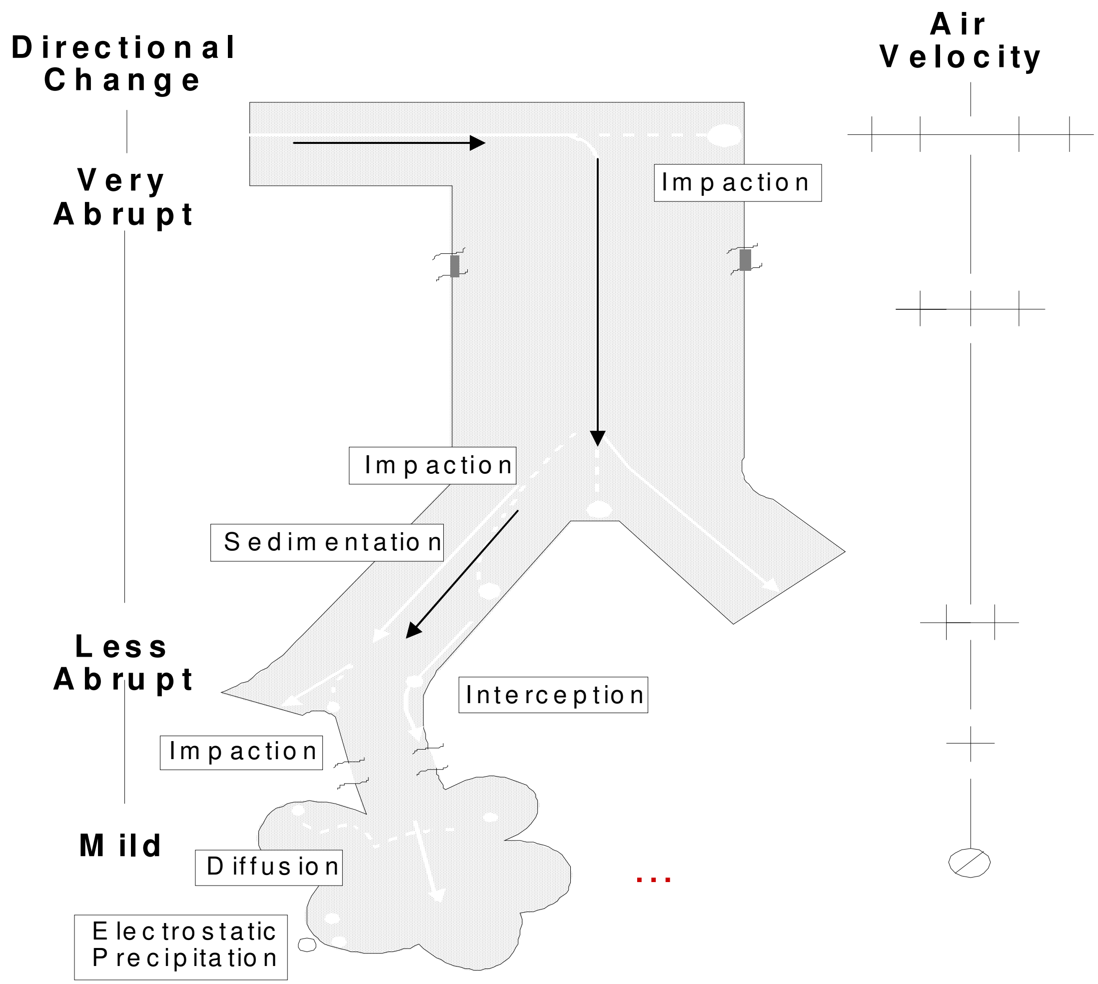
Model Structure: Physicochemical and Physiological Parameters

- Species-specific
- Inhalability
- Dissolution rates
- Ventilation rate
- Breathing mode
  - Nose only versus mouth
  - Activity patterns
- Mucociliary clearance rates
- Translocation rates

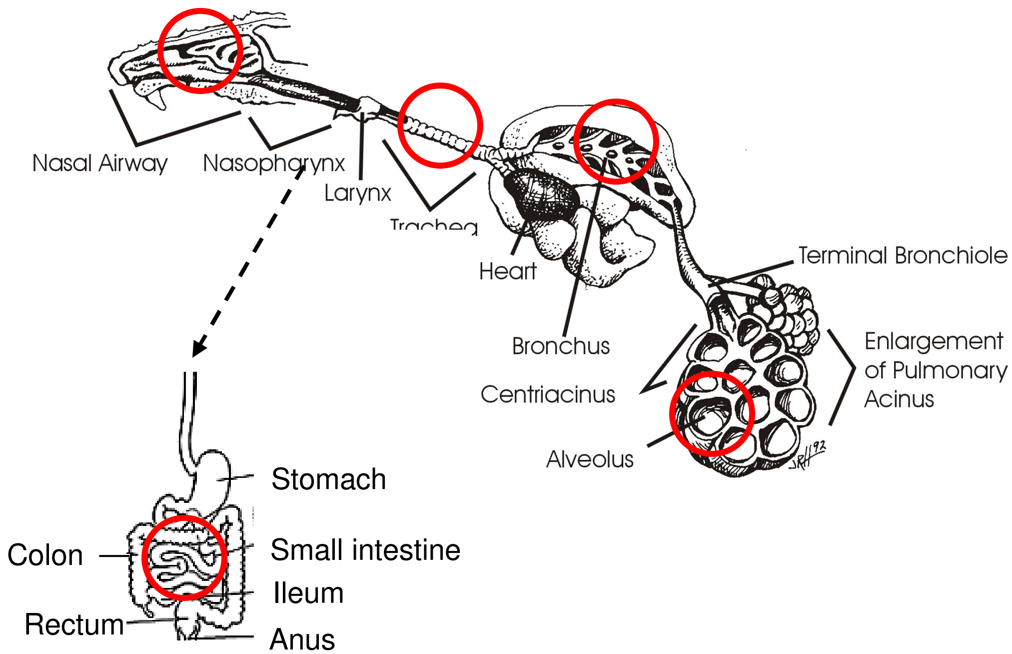
Construction Considerations: Deposition Mechanisms



Construction Considerations: Location of Deposition Mechanisms



Sample Sites to Support Dosimetry Model



- Sample at different times to track movement
- Determine rates to different locations
- Measure particle distribution and burden in each tissue
- Used to verify model structure and predictions

Example of Equations to Describe Deposition by Impaction in the Head

η (Imp) = $-0.014 + 0.023 \log (C_1\, \rho\, d^2_{ev} Q)\ (\mathrm{g}\ \mu\mathrm{m}^2\ \mathrm{sec}^{-1})^{-1}$

for $C_1\, \rho\, d^2_{ev} Q < 337\ \mathrm{g}\ \mu\mathrm{m}^2\ \mathrm{sec}^{-1}$

η (Imp) = $-0.959 + 0.397 \log (C_1\, \rho\, d^2_{ev} Q)\ (\mathrm{g}\ \mu\mathrm{m}^2\ \mathrm{sec}^{-1})^{-1}$

for $C_1\, \rho\, d^2_{ev} Q < 337\ \mathrm{g}\ \mu\mathrm{m}^2\ \mathrm{sec}^{-1}$

Where

$$C_1 = \frac{\left(\frac{3}{2}\right)\beta^{-\frac{2}{3}}}{\frac{0.383}{\ln 2\beta - 0.5} + \frac{1.233}{\ln 2\beta + 0.5}}$$

and $d_{ev} = d_f\, \beta^{1/3}$

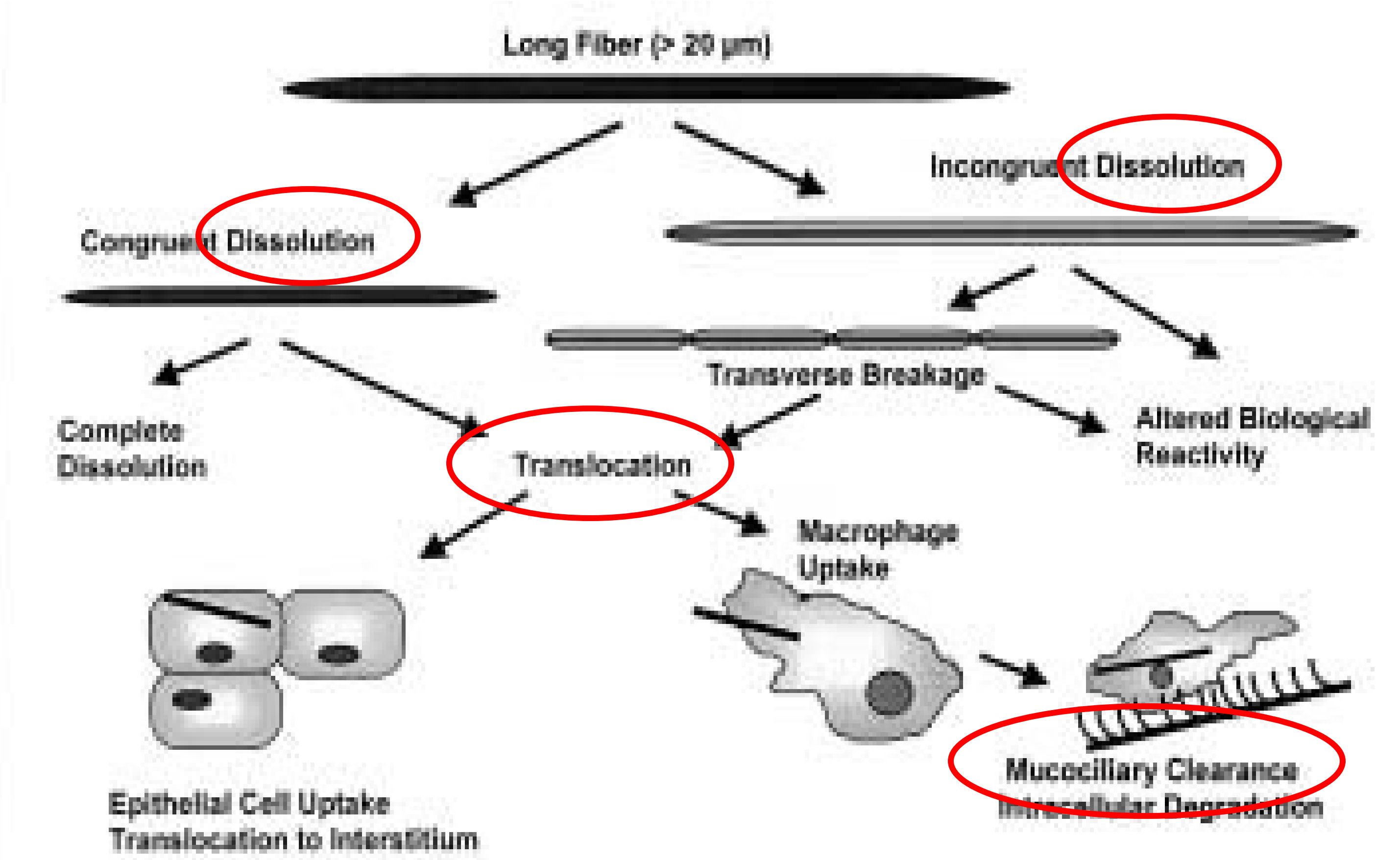
d_{ev} = Diameter of equivalent vol,

d_f = fiber diameter, and

β = fiber aspect ratio

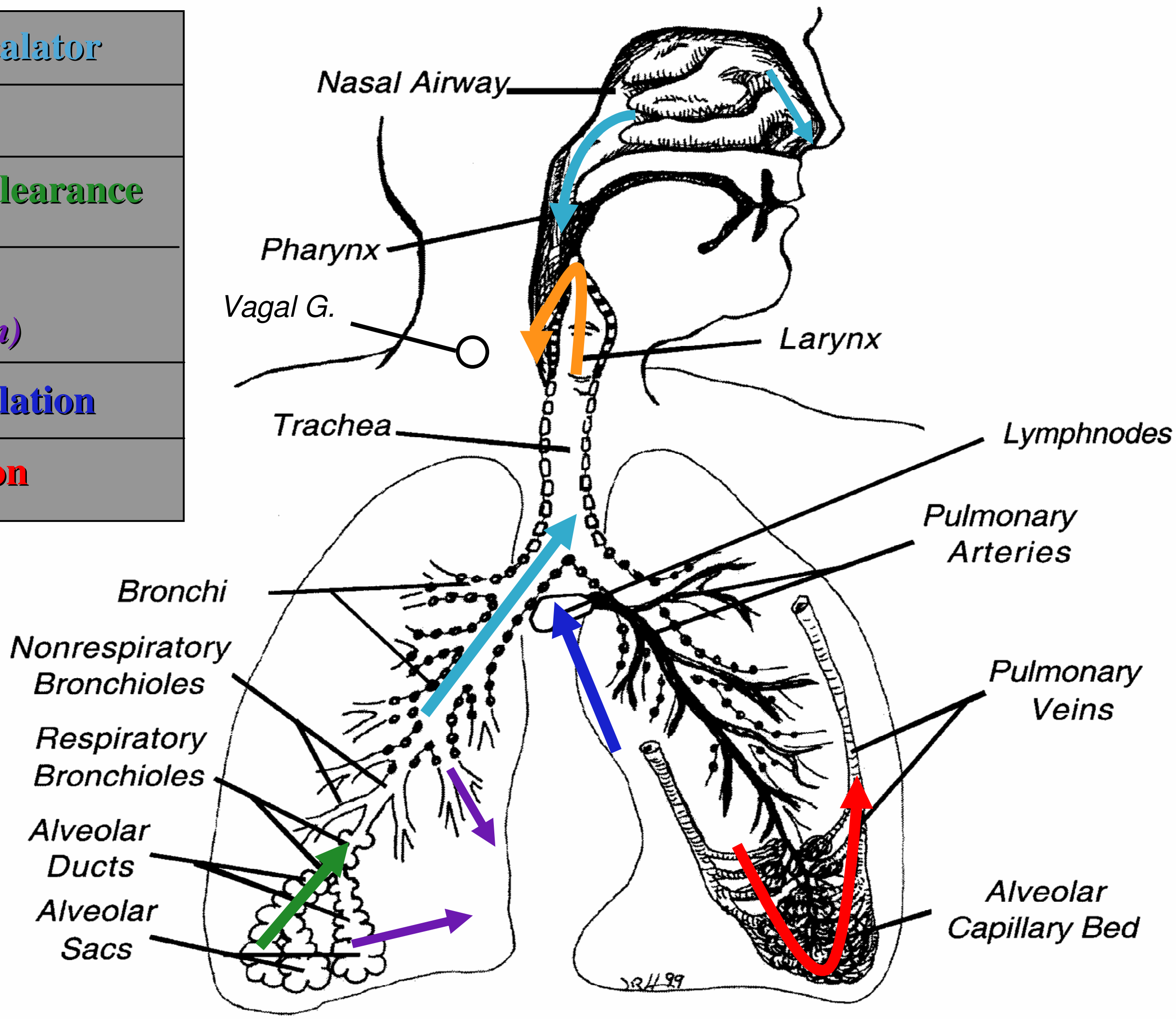
Accounts for fiber orientation & geometry

Construction Considerations: Clearance Mechanisms

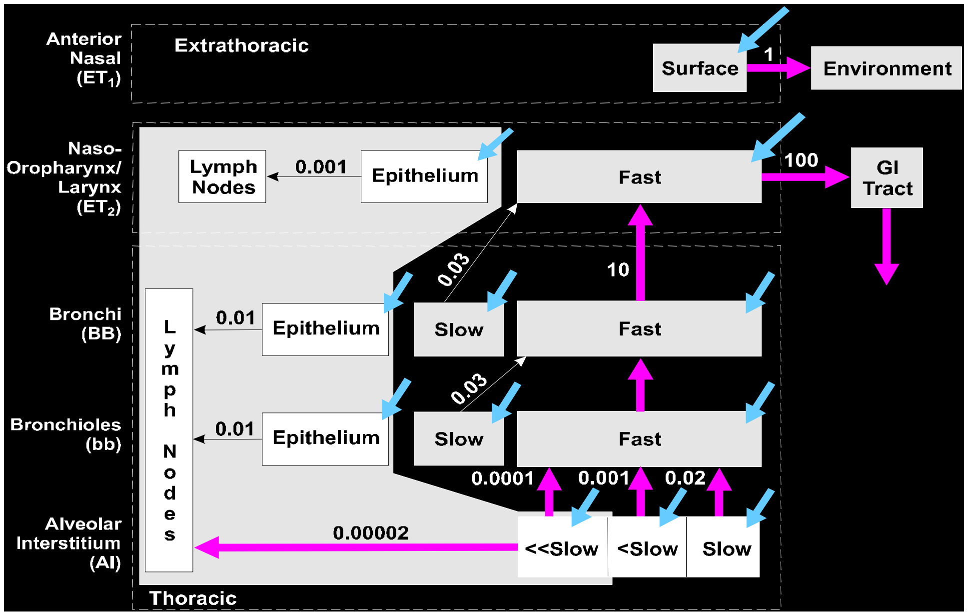


Construction Considerations: Location of Clearance Mechanisms

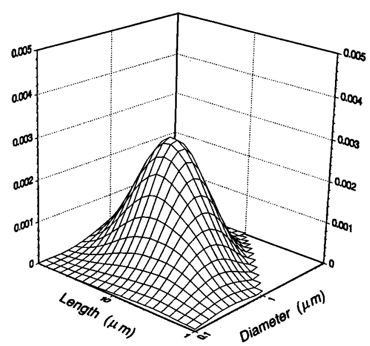
Mucociliary Escalator
GI Tract
AM-mediated Clearance
Interstitium (via Epithelium)
Lymphat. Circulation
Blood Circulation



Role in Risk Assessment: Putting it All Together

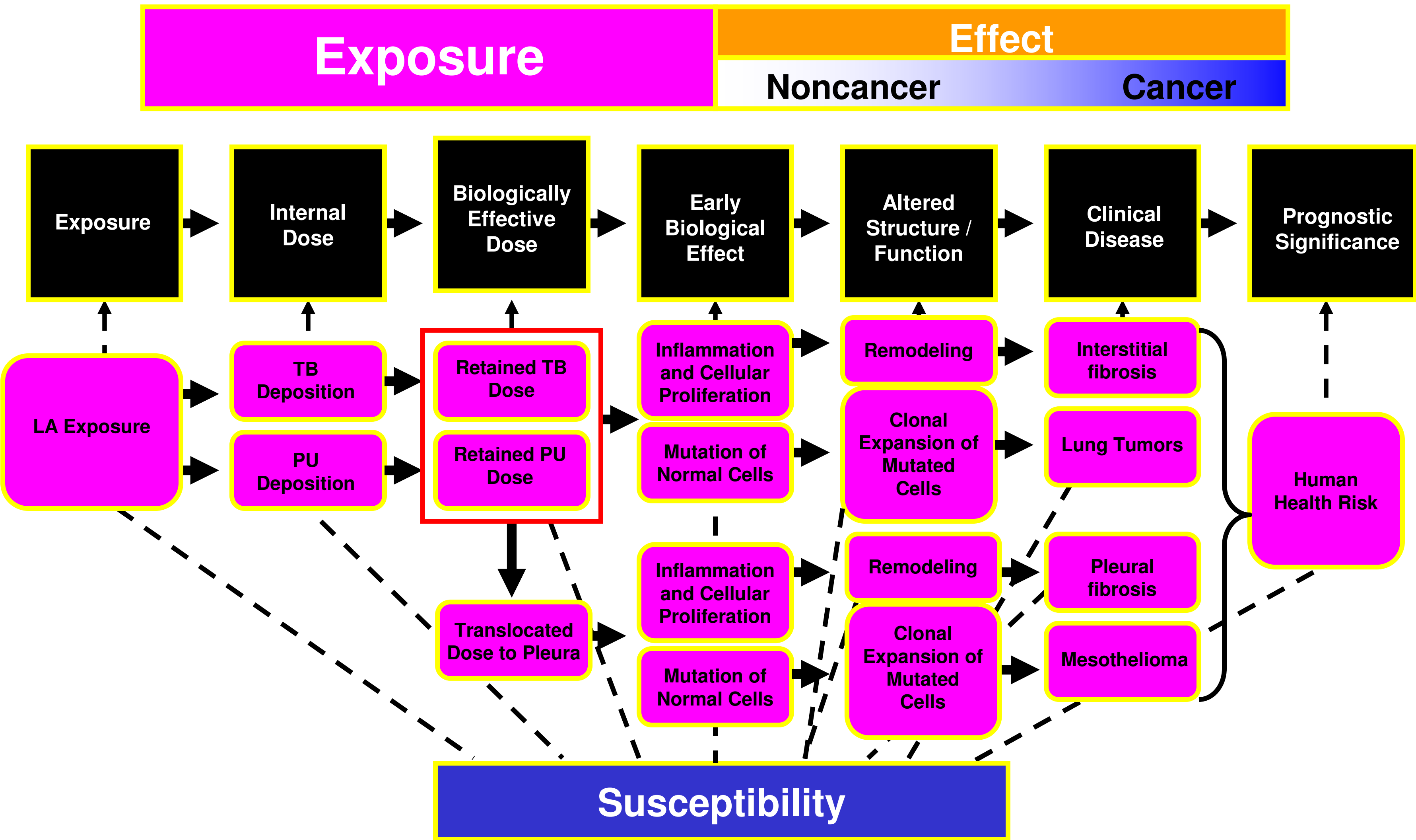


= air delivery
= clearance



- Simulate experimental regimen in rats
  - Exposure distribution
  - Duration
- Simulate human exposure scenarios
  - Exposure distribution
  - Activity patterns and duration
- Test hypotheses regarding different dose metrics
  - Size, Number or Mass or specific fraction of fibers, etc.
  - Normalized per respiratory region surface area, number of cells, etc.
  - Response analysis: Evaluate correlations of different dose metrics

LA *DRAFT*
Conceptual MOA Schematic



Dosimetry Modeling Advantages

- Aids interpretation and use of diverse data
- Predicts complex kinetic behavior
- Capability to “lump” or “split” model structure to predict range from regional to local tissue dose
- Translates laboratory animal data to reconcile with human data
- Flexibility to simulate different human activity patterns
- Explores systematically the factors responsible for potency across fibers
- Facilitates hypothesis generation
- Identifies areas of needed research

Summary

- External exposure ≠ internal dose
- Model builds on understanding of biological mechanisms
- Regional to local estimates of internal fiber burden to compare with disease endpoints and measurements
- Aid to comparisons across fibers and between species
- Refines risk assessment predictions